# A STUDY ON COMMON STD INFECTION IN INFERTILE FEMALE ATTENDDED TO INFERTILITY CLINIC HUSM, KOTA BHARU, KELANTAN





DR. NIK AHMAD ZUKY BIN NIK LAH

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Semua laporan kemajuan dan laporan akhir yang dikemukakan kepada Bahagian Penyelidikan dan Pembangunan perlu terlebih dahulu disampaikan untuk penelitian dan perakuan Jawatankuasa Penyelidikan di Pusat Pengajian.

USM R&D/JP-04

# LAPORAN AKHIR PROJEK PENYELIDIKAN
# R&D JANGKA PENDEK

## A. MAKLUMAT AM

Tajuk Projek: A study on common sexually transmitted disease infection in infertile Female attended to Infertility Clinic, HUSM, Kota Bharu , Kelantan.

No. Geran : 304/PPSP/6131201

Tajuk Program: _____

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Tarikh Mula: 1 hb Mac 2002


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☐ Penemuan asli/peningkatan pengetahuan

Kes jangkitan tularan seks (Chlamydia, Gonorrhea dan Syphilis) di kalangan wanita mandul dalam kajian adalah amat rendah. Infeksi Chlamydia Trochomatis telah didapati berlaku kepada 6 ( 4%) pesakit sahaja. Didapati tiada kejadian infeksi Gonorrhea atau Sifilis dalam sampel kajian . Semua ujian ulangan selepas rawatan antibiotik Azithromycin untuk infeksi Chlamydia Trachomatis menunjukkan keputusan yang negatif. Kadar penghapusan infeksi Gonorhea atau Sifilis tidak dapat ditentukan kerana tiada kejadian infeksi tersebut pada sampel kajian. Didapati terdapat hubungkait yang ketara dari segi statistik antara jangkitan infeksi Chlamidia Trachomatis dengan kerosakan salur falopion pada wanita mandul dalam kajian.

Prevalen Chlamidia Trachomatis ini tidak mewakili populasi sebenar rakyat Malaysia kerana kajian ini adalah dilakukan di sebuah hospital sahaja. Kajian yang lebih besar adalah diharapkan untuk mendapatkan gambaran yang lebih baik bagi mewakili rakyat Malaysia.

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**(i) LAPORAN/KERTAS PERSIDANGAN ATAU SEMINAR**

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## H. HUBUNGAN DENGAN PENYELIDIK LAIN

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**J. PELAJAR IJAZAH LANJUTAN**

*(Nyatakan jumlah yang telah dilatih di dalam bidang berkaitan dan sama ada diperingkat sarjana atau Ph.D).*

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**K. MAKLUMAT LAIN YANG BERKAITAN**

Pendiagnosan penyakit yang disebabkan oleh Chlamydia masih menggunakan Cara lama. Terdapat cara / kaedah yang lebih baik iaitu dengan menggunakan " LCR atau PCR". Diharap kaedah-kaedah ini dapat dilakukan di hospital HUSM dalam masa terdekat.

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**TANDATANGAN PENGERUSI**

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**PUSAT PENGAJIAN**

*Fn. My doc geran J/pendek*

# A STUDY ON COMMON SEXUALLY TRANSMITTED DISEASE INFECTION IN INFERTILE FEMALE ATTENDED TO INFERTILITY CLINIC HUSM, KOTA BHARU, KELANTAN

BY

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MD (USM)

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# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AIDS | - Acquired Immunodeficiency Syndromes |
| CDC | - Center for Disease Control |
| CMO's | - Chief Medical Officer's |
| C. trachomatis | - Chamydia trachomatis |
| DFA | - Direct Fluorescence Antigen |
| DNA | - Deoxyribonucleic Acid |
| EIA | - Enzyme Immunoassay |
| ELISA | - Enzyme Link Immunosorbant Assay |
| FCU | - First Catch Urine |
| FSW | - Female Sex Worker |
| HIV | - Human Immunodeficiency Virus |
| HUSM | - Hospital Universiti Sains Malaysia |
| LCR | - Ligase chain reaction |
| LGV | - Lymphogranuloma Venerum |
| LPS | - Lipopolysaccharide |
| MOMP | - Major Outer Membrane Protein |
| PCR | - Polymerase chain reaction |
| PID | - Pelvic inflammatory disease |
| RNA | - Ribonucleic Acid |
| SPM | - Sijil Pelajaran Malaysia |
| STD | - Sexually transmitted disease |

# ABSTRACT

| | |
|---|---|
| STPM | - Sijil Tinggi Pelajaran Malaysia |
| TPHA | - Treponema pallidum haemagglutination assay |
| TPI | - Treponema pallidum Immobilization |
| UK | - United Kingdom |
| VDRL | - Venereal Disease Research Laboratory |
| WHO | - World Health Organization |

# ABSTRACT

# Abstrak

**Pendahuluan:** Penyakit tularan seks, pada suatu ketika dikenali sebagai penyakit kelamin adalah diantara infeksi yang paling biasa di dunia ketika ini. Di negara-negara Barat didapati terdapat peningkatan yang dramatik terhadap insiden penyakit ini dalam jangkamasa 25 tahun. Adalah amat memilukan walaupun berbagai usaha untuk memerangi penyakit ini sejak tahun 1940 an dengan berbagai rawatan, penyakit ini masih wujud dan berkembang dalam abad ke dua puluh satu ini.

Peningkatan ini adalah dibantu oleh pematangan seksual yang awal pada remaja perempuan dan aktiviti-aktiviti seks yang awal yang berlaku dikalangan remaja. Selain itu faktor sosial seperti pemodenan, meningkatnya kebebasan dikalangan remaja dan kemudahan bergerak dimerata dunia membantu pada peningkatan insiden penyakit tularan seks ini. Malah pelancongan yang bermotifkan seks juga makin meningkat. Faktor ini juga membantu dalam penyebaran kepada penyakit tularan seks yang luar biasa dikawasan tropika dan juga peningkatan resistan antibiotik keatas penyakit tersebut.

Asalnya terdapat hanya lima penyakit yang diklasifikasikan sebagai penyakit tularan seks iaitu syphilis, gonorrhea, lymphogranuloma venereum, chancroid dan granuloma inguinale. Lymphogranuloma venereum adalah salah satu penyakit yang di sebabkan oleh Chlamydia trachomatis. Pada ketika ini terdapat lebih 20 jenis penyakit tularan seks atau penyakit yang boleh tersebar melalui seks, dimana masing-masing mempunyai manifestasi klinikal yang berlainan. Walaubagai manapun didalam kajian ini, kami hanya

memfokuskan kepada tiga jenis penyakit tularan seks iaitu infeksi chlamydia, gonorrhea dan syphilis. Infeksi chlamydia dan gonorrhea memang sudah dikenali sebagai penyebab kepada penyakit "pelvic inflammatory disease"(PID) dan kesan akibat penyakit ini seperti kemandulan, penyakit pelviks yang kronik dan kandungan luar rahim. Penyakit syphilis pula memberi kesan kepada keadaan bayi semasa dalam kandungan atau selepas kelahiran. Isu yang lain adalah infeksi chlamydia semakin meningkat di serata dunia.

**Objektif**: Untuk menentukan prevalen setempat ke atas organisma yang menyebabkan penyakit tularan seks seperti chlamydia, gonorrheoa dan syphilis pada wanita-wanita yang mendapat rawatan di Klinik Infertiliti Hospital Universiti Sains Malaysia, Kubang Kerian, Kota Bharu, Kelantan. Kajian ini juga bertujuan untuk mengetahui keberkesanan rawatan mengunakan antibiotik Azithromycin 1 gram keatas infeksi gonorrhoea dan *Chlamydia trachomatis*.

**Methodologi**: Kajian prospektif melibatkan 150 wanita yang mendapat rawatan di infertiliti klinik Hospital Universiti Sains Malaysia di antara 1 Mac 2002 hingga 28 Februari 2003. Sampel daripada endoservik diperolehi untuk mengesan infeksi *Chlamydia trachomatis* menggunakan ujian 'direct immunofluorescence', infeksi *Nisseria gonorrhoea* menggunakan kaedah 'Gram smear' dan 'culture dan sensitivity'. Darah juga diambil daripada mereka untuk ujian 'Venereal Disease Research Laboratory' (VDRL) dan untuk antibodi (Ig M) terhadap chlamydia. Jika ujian VDRL didapati positif, sampel darah kemudian diambil untuk ujian '*Treponema pallidum* haemagglutination assay' (TPHA).

Jika didapati wanita tersebut mempunyai infeksi *Chlamydia trachomatis* atau gonorrhoea atau kedua-duanya sekali, beliau dan suaminya akan dirawat dengan oral antibiotik azithromycin 1 gram sekali ambil sahaja. Selepas 2 minggu rawatan ujian-ujian seperti diatas akan diulangi untuk memastikan penghapusan infeksi tersebut. Jika ada dikalangan wanita tersebut didapati mempunyai infeksi syphilis beliau akan diberikan rawatan dengan intramaskular Bezanthine Penicillin 2.4 megaunit setiap minggu selama 3 minggu. Ujian ulangan TPHA akan dilakukan sebulan selepas dos yang terakhir.

**Keputusan**: Infeksi *Chlamydia trachomatis* telah didapati berlaku kepada 6 ( 4%) pesakit. Di dapati tiada kejadian infeksi gonorrhoea atau syphilis dalam sampel kajian. Semua ujian ulangan selepas rawatan antibiotic azithromycin untuk infeksi *Chlamydia trachomatis* menunjukan keputusan yang negatif. Kadar penghapusan infeksi gonorrhoea atau syphilis tidak dapat ditentukan kerana tiada kejadian infeksi tersebut pada sampel kajian.

**Rumusan**: Kes jangkitan tularan seks (*Chlamydia trachomatis*, gonorrhoea dan syphilis) dikalangan wanita mandul dalam kajian adalah rendah. Kadar penghapusan infeksi chlamydia oleh antibiotik azithromycin adalah bagus. Di dapati terdapat hubungkait yang ketara dari segi statistik antara jangkitan infeksi *Chlamydia trachomatis* dengan kerosakan salor falopian pada wanita mandul dalam kajian. Prevalen *Chlamydia trachomatis* ini tidak mewakili populasi sebenar rakyat Malaysia kerana kajian ini adalah dilakukan disebuah hospital sahaja. Kajian yang lebih besar adalah diharapkan untuk mendapat gambaran yang lebih baik bagi mewakili rakyat Malaysia.

## Abstract

**Introduction:** Sexually transmitted disease (STDs), once called venereal disease, are among the most common infectious diseases in the world. In Western countries, there has been a dramatic increase in the reported incidence of sexually transmitted diseases (STD) during the past 25 years. It is tragic irony that despite medical efforts against sexually transmitted diseases and the existence, since the 1940s, of powerful treatments for them, these diseases persist; even thrive in the twenty first century.

This trend was augmented by earlier sexual maturity in girls and earlier age of onset of sexual activity in both sexes. Other sociological changes which contribute to the increased incidence of STD include urbanization, increased mobility among the young, and the greater ease of world-wide travel. Sexual tourism is increasingly common. This last factor has also promoted the importation of unusual tropical STDs and antibiotic-resistant infections.

Traditionally, five diseases have been classified as sexually transmitted diseases which are syphilis, gonorrhoea, lyphogranuloma venereum, chancroid, and granuloma inguinale. Lyphogranuloma venereum is one of disease caused by Chlamydia thrachomatis. To date more than 20 distinct sexually transmitted or transmissible pathogens were identified which may have different clinical manifestations. However in this study we are only concentrate on three common sexually transmitted diseases which are chlamydial infection, gonorrhoea and syphilis.

Chlamydial infection and gonorrhoea are well known to cause pelvic inflammatory disease (PID) and their sequelae; infertility, chronic pelvic pain and ectopic pregnancy, whereas syphilis affect the outcome of the baby before and after the pregnancy. Another important issue is that, the genital chlamydial infection is increasing in trend worldwide.

**Objectives:** To determine the local prevalence of common organism in Sexually Transmitted Diseases (STDs) infections (*Chlamydia trachomatis*, gonorrhoea and syphilis) in infertile females attended to Infertility Clinic Hospital Universiti Sains Malaysia, Kubang Kerian, Kota Bharu, Kelantan. And to determine the clearance rate of *Chlamydia trachomatis* and gonorrhoea infection after a course of azithromycin 1 gram single dosage.

**Methodology:** This is a prospective study involving 150 infertile females under follow up at infertility clinic Department of Obstetrics and Gynaecology, Hospital Universiti Sains Malaysia between 1st of March 2002 till 28th of February 2003 . Endocervical samples were obtained to detect *Chlamydia trachomatis* by direct immunofluorescence, *Neisseria gonorrhoea* by Gram smear and culture & sensitivity. Blood samples were also obtained for Venereal Disease Research Laboratory (VDRL) testing and for Ig M antibody toward chlamydia.

For VDRL testing positive patient another blood sample for *Treponema pallidum* haemagglutination assay (TPHA) will be taken. In a patient with a positive Chlamydia trachomatis or gonorrhoea or both infections, she and her partner will be treated with a

single dose of azithromycin 1 gram orally. After 2 weeks of azithromycin, the respective investigation(s) will be repeated to determine the clearance of such infection(s). In a patient who was positive for syphilis she will be treated with intramuscular Benzanthine Penicillin 2.4 Megaunit 3 doses. A repeated TPHA testing will be carried out after a month of completed treatment.

**Results:** *Chlamydia trachomatis* infection was present in 6 (4.0%) patients. There was no incidence of gonorrhoea or syphilis infection in the studied population. All repeated investigations after azithromycin for *Chlamydia trachomatis* infection showed a negative testing. The clearance rate of gonorrhoea or syphilis is unable to determine as there is no incidence of such infections in the studied group.

**Conclusion:** The prevalence of sexually transmitted diseases (Chlamydia trachomatis, gonorrhoea and syphilis) infection in infertile female is low in our studied group. The clearance rate of *Chlamydia trachomatis* infection by azithromycin is good. There is statistically significant correlation between the incidences of tubal factor causing infertility with Chlamydia trachomatis infection among them. The prevalence is not a true representation of Malaysian populations as it is a hospital-based study. A larger scale study involving a few centers is needed in order to obtain a better representation of Malaysian populations.

# INTRODUCTION

# I. INTRODUCTION

## 1. Sexually Transmitted Diseases (STDs)

### 1.1 Epidemiology

Sexually transmitted diseases and sexually transmissible infections are two terms that are synonym. They have replaced the older terminology, venereal disease. Traditionally venereal diseases referred to gonorrhoea, syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale. The concept now is that any microbial agent or syndrome that is passed from person to person through close intimate contact qualifies as an STD (Spence MR 1989). This redefinition expands the previous list of five venereal diseases to a more extensive list of organisms and conditions they cause.

Not all STDs are reportable, and even reportable diseases are seldom reported completely. Data from most of the world are sketchy, occasionally based on prospective cohort studies of incidence, or on serially repeated prevalence surveys, but more often based on sporadic prevalence survey. Populations sampled in developing societies most often have included STD clinic patients or family planning clinic patients, who are not representative of the total population. Prenatal samples generally best represent fertile married women of reproductive age who seek prenatal care, they often under represent the single women who are at higher risk and under represent women rendered infertile or subfertile by past or present STDs.

There was one study by World Health Organization (WHO) estimating number of cases and annual incidence of syphilis, gonorrhoea, chlamydial infections and trichomoniasis, based on the prevalence of STDs from various populations in clinical survey. The study showed that the overall estimated number of new cases of these four STDs for males and females age 15 to 49 totaled 333 million, with 12.2 million cases of syphilis, 62.2 million of gonorrhoea, 89.1 million of chlamydial infections and 167.2 million of trichomoniasis. These estimates suggest that 90 percent of these STDs are in developing countries (Gerbase AC et al 1998).

In general, data on reported STDs from North America and many countries of Europe, as well as from Australia and New Zealand showed steady increases in the incidence of all STDs during the 1960s, with decline of most of the bacterial STDs but continual increases in viral STDs and genital chlamydial infections during the 1970s and 1980s. In this industrialized countries, the incidence of gonorrhoea and syphilis began to decline at different times, and declined at different rates and have continued to decline during the 1990s (Sevgi O. Aral et al 1999). In the Southern Hemisphere, a few regions such as Costa Rica, Thailand and Zimbabwe have experienced declining rates of bacterial STDs during the 1990s. In contrast, some countries such as China, Mongolia, Russia are experiencing explosive epidemics of bacterial STDs. However many countries in Eastern Europe, Southern Africa and Asia continue to experience epidemic increases in HIV infection (Cohen M et al 1996, Tichonova L et al 1997).

From literature reviewed, the frequency of disease is dependent on various factors such as the geography of an area, microbial factors, host response and latent infections (Spence MR 1989). Another factors, are urbanization, prostitution, mobility and care facilities to the STDs patients (Georg M Antal 1987). An example for geography of an area; chancroid caused by *Haemophilus ducreyi* is frequently encountered in tropical and subtropical regions. This is in contradistinction to gonorrhoea, which is worldwide in its distribution and prevails as an endemic problem. However with a modern transport and a new trend of international travel these diseases can easily widespread worldwide.

Another factor is, organism characteristics, such as dividing time, can be an important factor regarding both the transmission of infection and the perception of disease prevalence. The incubation period of Neisseria gonorrhoea for men varies between 1 to 14 days, the mean time approximating 2 to 5 days (Harrison WO et al 1979). Unfortunately, these data apply to only patients who become symptomatic. Another example is syphilis; the incubation time for syphilis varies between 10 and 30 days, with the mean time being 3 weeks.

Spence M R, reported that the ability to transmit an infectious agent from one person to another is directly proportional to the size of the inoculum and the virulence of the organism (Spence MR 1989). Patient awareness of the disease is also important. Two important factors of body awareness include body site involved and decreased concern of the host. An example of this would be the woman with gonococcal cervicitis. This lesion may produce a minimal degree of lower abdominal pain, as well as a slight change from

normal in the vaginal secretions. The women may disregard these symptoms as unimportant and not relate them to an STD, which could result in continuous transmission of infection as well underreporting of disease owing to the failure of the infected person to seek medical attention. To make things worse, some sexually transmitted organisms possess the property of latency. The two organisms with this property are herpes simplex virus (HSV) and HIV (Spence MR 1989).

## 1.2 Risk Factors

Genital tract pathogens are transmitted bidirectionally between men and women. However, the infections that are transmitted through infected secretions for examples, gonorrhoea, chlamydia and HIV are transmitted disproportionately more frequently to women than to men. Therefore, gender can affect a person's risk of acquisition of an STD. Other risk factors for STDs that must be considered include age, sexual behaviour, ethnic origin, socioeconomic status and form of contraception

### 1.2.1 Age

STDs are problems of the young. Although they are not limited to this group, from literature reviewed in the United State, about 50 percent of teenager (15 to 19 years of age) reported in 1995 that they had ever had sexual intercourse, compared with 53 percent in 1988 and 47 percent in 1982. Comparing to other parts of the world, the sexual activity among adolescents in Africa, the Caribbean and to some extent in South America has become increasingly common. A study on about 1500 adolescents in Monrovia, Liberia (Woods ET et al 1985) revealed that among adolescents age 14-17 about half of the girl and 75% of the boys were sexually experienced. Among sexually experienced females, approximately 10% of those age 14-17 and about 20% of those age 18-21 reported that they had had an STD. The reason for the increase incidence of the STDs is, this group has been progressively more sexually active, and possibly its member are less

selective in sexual partners. Additionally their knowledge base regarding transmission and prevention of infection have all enhanced the problem.

In addition, age at sexual debut has been independently associated with the development of cervical cancer in some studies, and in other studies with C. trachomatis antibody prevalence and with HIV infection, perhaps owing to the biological development of the female cervix during the teenage years (Sanchez J et al 1996)

### 1.2.2. Sexual behaviour and prostitution

The risk of exposure to an STD is directly associated with number of infected sex partners. The number of sex partners within a specific time period, often 1 to 3 months, has been shown to be a risk factor for having gonorrhoea, chlamydia, genital herpes, and human papillomavirus infections (D'Costa LJ et al 1985, Handsfield HH et al 1986). Lifetime number of sexual partners is associated with the risk of cervical and other genital cancers, as well as with the prevalence of serum antibody reflecting past exposure to various STDs. However, the relationship between number of sex partners and STD risk is not simple, it is of course influenced by the partner's sexual behaviour and the varying infectiousness of infected partners (Sevgi O. Aral and King K. Holmes 1999). Married women in stable, mutually monogamous sexual relationships appear to be at essentially no risk for the acquisition of an STD. The single person with more than one sexual

partner is obviously at high risk, the risk of acquiring an STD increasing with increasing numbers of partners.

In six African countries surveyed in 1988 to 1990, the percentage of respondents who had engaged in casual or commercial sex in the last 12 months ranged from 8 to 44 percent for men, and 2 to 17 percent for women, with the percent of men engaging in such behaviour two to four times higher than the percent of women in five of the countries (Carael M et al 1991). A study by the WHO found that in the Ivory Coast, Lesotho, Togo and Kenya from 8 to 13 percent of sexually active men in the general population reported purchasing sex from a female sex worker (FSW) in the previous year (Carael M et al 1991). On a global basis, commercial sex has been most common in settings characterized by poverty, social disintegration, and a double standard of sexual behaviour (e.g., Latin American countries).

Where many of these factors coincide, commercial sex is most prevalent (Day S 1988). Commercial sex and FSW contact are clearly major factors in the epidemiology of HIV and other STDs in many developing countries of Africa, Asia, and Latin America (Sanchez J et al 1996, D'Costa L J et al 1985, Handsfield H H et al 1986, Ryan C A et al 1998). In such settings, the great majority of STD clinic attendees are male, and the majority of those with gonorrhoea, syphilis, or chanchoid identify the suspected source contact as a FSW. A study from Thailand, among a general population group of 1,100 young men in northern Thailand indicated that three quarter of them had paid for sex from a FSW at some time (Nopkesorn T et al 1993).

### 1.2.3. Socio-economic status, occupation

Sexually transmitted diseases affect all social classes. Although STDs are associated with poverty and lack of education and living in overcrowded slums, the rich also suffer from these diseases. However, certain occupations are more at risk to exposure and poor treatment. Barmaids, taxi-drivers, soldiers, sailors, hotel staff, night club girl are all well documented high risk groups; they often work in or be at frequent high risk places, such as bars, night club and cheap lodgings. Among the group is long distance truck drivers in which was reported as purchasing sex from sex worker much more frequently (Carswell JW et al 1989).

## 2. STD and infertility

Sexually transmitted diseases (STDs) are well known to affect human fertility primarily through infections of upper genital tract caused by microorganisms that ascend from the cervix or vagina. These will give rise to a spectrum of disease known as Pelvic inflammatory disease (PID).

The PID comprises a spectrum of upper genital tract inflammatory disorders among women that includes any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis (Anonymous 1993). Salpingitis, is an inflammation of the epithelial surfaces of the fallopian tubes caused by active infection with one or more of a number of organisms, most of which are sexually transmitted and ascend along mucosal surfaces from the cervix to the endometrium to the salpinx and, in some women, to the peritoneum (Kahn JG et al 1991) and this salphingitis or infection of the fallopian tubes is the most important feature of PID. However in one study by Jacobson L et al, about two-thirds of women with a clinical diagnosis of PID in fact have salpingitis, while remaining one-third have either conditions or normal pelvic organs when laparoscopy is used to confirm a clinical diagnosis (Jacobson L et al 1969).

Women with PID present with a vast array of clinical manifestations that range from virtually none to severe. In fact, about two-thirds of cases of PID probably go unrecognized (Sellors JW et al 1988).

Infertility usually is defined clinically as the lack of recognized conception after 1 year of regular intercourse without the use of contraception. in the general population, the conception rate is 10 to 15 percent per cycle, whereas in couples who have been infertile for 1 year, it is 5 to 6 percent per cycle (Lenton EA et al 1977). If infertility has persisted for 2 or more years, the conception rate falls markedly to about 1 to 3 percent per cycle (Collins JA et al 1983). In population-based studies of infertile couples, eventual pregnancy rate varied from 40 to 75 percent up to 10 years after the initial diagnosis (Collins JA et al 1979, Hull MG et al 1985, Schmidt L et al 1995). Tubal infertility refers to infertility caused by damaged fallopian tubes, which can result from salpingitis, endometriosis, pelvic surgery, or congenital causes. We will address infertility only as it relates to salpingitis.

The presence of tubal damage can be identified only in women who are evaluated by a specialist. This is because the diagnosis is needs to be confirmed by evidence of obstruction by hysterosalpingography or virtually by using laparoscopic procedure. In which such evaluations only be provided in established hospital and usually are expensive. Therefore not all patients underwent the procedures, and as a result the prevalence of tubal infertility is probably under estimated.

In a study in Bristol, England, an average of 1.2 couples per 1000 population annually requested infertility advice from a specialist (Hull MG et al 1985) At this rate, approximately 1 in 6 couples (with an average length of infertility of 2.5 years) would seek help from a specialist at some time in their lives. Tubal damage was demonstrated in

14 percent of these infertile couples. In a representative Denmark populations, nearly half of infertile couples had sought infertility services. One in five were diagnosed with tubal infertily, with older women (age > 35 years) having higher rate (Schmidt L et al 1995)

Internationally, the WHO multicenter study compared STD-related infertility in five different regions of the world (Cates W et al 1985). More than 8000 infertile couples were enrolled in the study, and more than 6000 (71%) completed evaluation of the fallopian tube. Almost two-thirds of infertility in African women was attributed to infection, including 49 percent with bilateral tubal occlusion and 24 percent with pelvic adhesions. The prevalence of tubal occlusion in Africa was more than three times that of any other region. Developed countries had an 11 percent prevalence of tubal occlusion in infertile women. Non African developing areas had higher rates of tubal occlusion that developed countries, although well below those of Africa.

Another approach to estimating the prevalence of tubal infertility utilizes extrapolation from the annual reported incidence of STDs (Cates W et al 1999). For example, approximately 3 million lower genital tract infections with chlamydia and/or gonorrhoea occur in women each year in the United States (CDC, 1997). Assuming 30 percent of these cause salpingitis leads to tubal occlusion, an estimated annual incidence of 125,000 cases of STD related infertility occur each year (Westrom L 1985). Converting these to cumulative numbers, they estimated that approximatedly 2 million reproductive-age women (range 200,000 to 2.7 million) currently have tubal occlusion in the United States.

In long-term follow up studies in Lund, Sweden, about 11 percent of women with laparoscopically documented acute salpingitis subsequently became infertile owing to tubal occlusion as compared with none of the control women with similar pelvic symptoms but noninflamed fallopian tubes (Westrom L. et al 1992). The percentage of those with tubal infertility after PID was similar in women age 25 years or older (12 percent) compared to younger women (11 percent). In his study the incidence of subsequent tubal infertility is approximately 8% after one episode of pelvic infection, 19% after two episodes, and 40% after three episodes.

# 3. Common STD organisms

## 3.1 Chlamydia

### 3.1.1 Overview

Chlamydial infections of the genital tract have a worldwide distribution, and are prevalent in both industrialized countries and in the developing world. The World Health Organization (WHO) estimates that 89 million new cases of genital chlamydial infections occurred worldwide in 1995 (WHO, 1995). It is the commonest sexually transmitted bacterial pathogen in Britain (Government Statistical Service, England 1996). It is also the most common bacterial sexually transmitted infection in the United States (CDC, United States, 1997). It causes urethritis and epididymitis in men, and cervicitis, salpingitis, and endometritis in women. Symptoms of lower genital tract infection in both sexes can be mild or non-specific. Up to 70% of infections in women may be asymptomatic and are thus unlikely to be treated (Schachter J, et al 1983). Infected women can pass the infection on to their children at birth.

Among women, this infection may cause important long-term sequelae including tubal infertility, ectopic pregnancy and chronic pelvic pain (Cates W. et al 1991). These complications occur in up to 25% of cases of chlamydial pelvic inflammatory disease (Trachtenberg AL et al 1988). Scholes et al have shown that screening for asymptomatic infections in women results in a reduction of 56% in the incidence of Pelvic Inflammatory Disease (Scholes D et al 1996).

Because of asymptomatic features of infections, efforts to control Chlamydial infection have been aided in recent years by the development of screening criteria for use in situations where there is a low prevalence of infection (Handsfield HH et al 1986, Phillips RS et al 1989, Stergachis A et al 1993). A randomized, controlled trial have showed that selective testing and treating women at increased risk for cervical chlamydial infection was associated with a reduced incidence of PID ( Delia Scholes et al 1996)

A number of methods have been developed for detection of chlamydial infection, which varies in sensitivity and specificity. No single method has yet gained general acceptance (Beagley and Timms, 2000). The selection of a diagnostic test for detection of chlamydial genital infection depends on availability, local expertise and prevalence of *Chlamydia trachomatis* in the test population. Cell culture, although being the most sensitive and the gold standard, is too expensive in non endemic regions and is not widely available, so the use of non culture technique is very attractive. The other technique include antigen detection, nucleic acid probes, cytology and serology (Carolyn M Black 1997)

The two common techniques for antigen and antibody detection are enzyme immunoassay (EIA) and direct fluorescent antibody (DFA). Direct fluorescent antibody (DFA) employs fluorescent labeled monoclonal antibody against major outer membrane proteins, which present in all chlamydial serovars and throughout their life cycle. Previous studies has shown this technique to be both specific and sensitive, minus the labour intensiveness needed for isolation of Chlamydia in cell culture ( Tam MR et all

1984,Thomas BJ et al 1984, Stamm W E et al 1984, Baselski V S et al 1987, Taylor-Robinson D et al 1991)

As a conclusion the efficiency of screening strongly depends on the prevalence of infections in the target population and availability of techniques of chlamydial detection. As there is still a lack of estimates of the prevalence of asymptomatic infections in our general population as there is not many effort have been done to it, therefore this study will help to estimate the incidence of prevalence of *Chlamydia trachomatis* infection in our community.

### 3.1.2 Historical Events

The genital tract infections, such as non gonococcal urethritis and neonatal ophtalmia caused by *Chlamydia trachomatis* were not recognized until it was possible to categorize these conditions, following the identification of the gonococcus. It was first visualized in 1907 by Halberstaedter and Prowazek in stained conjunctival scrapings taken from 'orang utans' that had been inoculated with human trachomatous material. Shortly thereafter, similar inclusions were identified in human material from trachoma cases and then in conjunctival scraping taken from infants with inclusion blennorrhea. Inclusions were then found in the genital tracts of mothers of the affected infants and in the urethras of the fathers.

In the first decade of that century the presence of these inclusions was associated with non gonococcal urethritis. The first isolate of chlamydia from the genital tract was made in 1959 by Jones, Collier, and Smith, who recovered *Chlamydia trachomatis* from the cervix of the mother of an infant with ophthalmia neonatorum (Jones BR et al 1959).

In 1965 Gordon and Quan developed a tissue culture isolation procedure for *Chlamydia trachomatis* (Gordon F et al 1965). This have made possible to screen large number of specimens and obtain the result of an isolation attempt in 48 to 72 hours, which made the diagnosis clinically useful. Page in 1966 reviewed the microbiology of *Chlamydia trachomatis* and classified them as bacteria. Since 1984 some rapid diagnostic techniques for *Chlamydia trachomatis* have become available, among them are a direct specimen test with monoclonal antibodies (immunofluorescence test, enzyme-linked immunoabsorbent assay (ELISA) and a recombinant DNA technique.(Stamm WE et al 1984).

### 3.1.3 Effect and Sequelae

Genital infections caused by *Chlamydia trachomatis* closely parallel those owing to *Nisseria gonorrhoea* in terms of clinical manifestations. Both organisms preferentially infect columnar or transitional epithelium of the urethra, with extension to the endocervix, endometrium, fallopian tubes, and peritoneum. Both organisms can produce extensive subepithelial inflammation, epithelial ulceration and scarring. Rarely, both organisms can produce systemic manifestation. In general, infections caused by

*Chlamydia trachomatis* tend to be less abrupt in onset and are more often characterized by no symptoms or by milder symptoms than in the case for gonococcal infection.

**Cervicitis**

Although many women with chlamydia isolated from the cervix have no signs or symptoms of infection, at least a third generally have a local signs of infection on examination (Paavonen J et al 1988). Most commonly found are mucopurulent discharge (37% of women) and hypertrophic ectopy (19%). Hypertrophic ectopy refers to an area of ectopy that is edematous, congested and bleeds easily. Women who exhibit signs of chlamydial cervicitis (mucopurulent discharge, hypertrophic ectopy) yield greater numbers of chlamydial inclusion forming units on primary isolation in tissue culture than women who have chlamydial infection without cervicitis (Hobson D et al 1980).

The prevalence of *Chlamydia trachomatis* infection is greater in women with ectopy than in those without ectopy (Richmond SJ et al 1980). Ectopy may predispose women to chlamydial infection by exposing a greater number of susceptible columnar epithelial cells, making infection more likely on exposure. Unfortunately, the majority of women with chlamydial infection cannot be distinguished from uninfected women by clinical examination and thus require the use of specific diagnostic testing.

Nearly all women with endocervical chlamydial infection have or develop antibodies to *Chlamydia trachomatis* in serum as assessed by the micro-Immunoflourecence assay (Richmond SJ et al 1980). Sequential culturing of untreated women has demonstrated that chlamydial infection of the cervix may persist for weeks or months without development of symptoms, or may spontaneously resolve (McCormark WM et al 1979).

**Endometritis and Salpingitis**

*Chlamydia trachomatis* infection can spread from the cervix to the endometrium, producing endometritis, and to the fallopian tubes, producing salpingitis (Mardh et al., 1976). Mardh and colleagues found that 19 of 53 women with salpingitis had chlamydia infection of the cervix and that of those with cervical infection who had laparoscopy, six of seven grew *Chlamydia trachomatis* in a culture from the fallopian tube. Upper genital tract spread occurs in 10-40% of women with cervical chlamydial infection. Other serologic studies of women with salpingitis also suggest a prominent etiologic role of Chlamydia (Treharne JD et al 1975). Studies in Seattle in women with laparoscopically confirmed salpingitis and histologically confirmed endometritis indicate that 80 to 90 percent have proven chlamydial or gonococcal infection, with the proportion having either Chlamydial or gonococcal infection being approximately equal (Eschenbach DA et al 1975). Many cases of chlamydial salpingitis are associated with mild or absent symptoms or signs, despite progressive tubal scarring, resulting in infertility (Mardh PA 1986).

*Chlamydia trachomatis* spreads to upper reproductive tract can occur either from subclinical cervical infection or from mucopurulent cervicitis. Spread to the endometrium can also occur after therapeutic abortion or following vaginal delivery, causing late onset postabortal or postpartum endometritis.

### 3.1.4. Diagnostic methods

Being an intracellular pathogen *Chlamydia trachomatis* requires a cell culture system for propagation in the laboratory. Thus, cell culture has been the gold standard test for the detection of *Chlamydia trachomatis* for years.(Schacter J et al 1995). However, the requirements both in terms of technical expertise and specimen transport make cell culture impractical in setting in which neither a cold chain nor a cell culture can be maintained. They must be placed in specific transport media and refrigerated until they are inoculated within 24 hours onto cell culture plates. Therefore, It is time consuming and laborious and can therefore be provided by only a few central laboratories.

The development of nonculture tests has been a major research priority over the last 15 years due to the inadequacies, cost, and technical difficulties of cell culture. Many nonculture diagnostic tests for *Chlamydia trachomatis* are now commercially available. The first of these tests used antigen detection, generally of Chlamydia lipopolysaccharide (LPS) as a means of detecting chlamydial elementary bodies in genital specimens. The most widely used of these assays are the direct immunofluorescence assays (DFA) and enzyme-linked immunosorbent assays (EIA) tests. In general, when obtained from the

cervix, these tests detect between 60 and 85 percent of infections relative to culture. (Black CM 1997).

In DFA, fluorescein conjugated antibodies directed against either the LPS or the major outer membrane protein (MOMP) component react with the Chlamydia surface. The fluorescein can subsequently be visualized by fluorescence microscopy. Because the size of the extra cellular elementary bodies is close to the resolving power of the microscope, DFA requires skilled personnel in order to differentiate C. trachomatis organisms from non-specific fluorescent particles. The diagnostic performance of DFA is therefore highly dependent of the number of organisms that should be seen in order to obtain a positive result (Thejls H et al 1994).

When it is done by an experienced technician, it has a sensitivity of 80 to 85 percent, but overall sensitivity depends both on the experience of the person performing the test and on collection of an adequate specimen (Stamm WE et al 1984). The specificity of DFA is more than 99 percent. DFAs can be considered in settings where costs are a major issue.

The sensitivity of the EIAs generally are in the range of 60 to 80 percent compared with culture, and vary by assay. However, it requires a confirmatory assay with a blocking antibody or with DFA to eliminate false positive results.

The most exciting recent development in chlamydial diagnostic testing has been that of automated methods for the detection of amplified *Chlamydia trachomatis* DNA or RNA.

The two most widely used methods are ligase chain reaction (LCR) and polymerase chain reaction (PCR), both of which can be used for cervical, urethral, and urine specimens from males and females. The LCR and PCR target nucleotide sequences on the plasmid of *Chlamydia trachomatis*, which is present in multiple copies within each elementary body. The specificity of these tests has consistently been above 99 percent (Schachter J et al 1995). The sensitivity of LCR performed on endocervical specimens has ranged from 81 to 100 percent (Schachter J et al: 1995, Schachter J et al 1996). and on first catch urine in female (FCU) is 69 to 96% (Chernesky MA et al 1994, Ridgway GL et al 1996, Schachter J et al 1995, Lee H et al, 1995). The sensitivity of PCR on the fresh catch urine (FCU) has demonstrates 82-93 percents (Pasternack R et al 1996) and on endocervical swab is around 60 to 92 percents (Toye B et al 1996, Bianchi A et al 1994, Pasternack R et al 1996).

### 3.1.5. Treatment

Currently, many effective drugs are available for treating chlamydial infections. The choice of antimicrobial agents should be based on efficacy, side effects, compliance, and the cost. The most active drugs against *Chlamydia trachomatis* in tissue culture are the tetracyclines, followed by macrolides, sulfonamides, some fluoroquinolones, and clindamycin. Tetracyclines are effective against *Chlamydia trachomatis* and have been the recommended treatment for chlamydial infection for 20 years. The efficacy of the various tetracyclines is similar, with failure rates ranging from 0 to 8% (Weber JT et al 1995).

The choice is based on their plasma half life and their side effects. Tetracycline hydrochloride administered at a dosage of 500 mg fours times daily or 250 mg three times daily for 7 days provides comparable bacteriological cure rates (Bowie WR et al 1980). Newer tetracyclines, minocycline and doxycycline have longer half-lives, they are as effective as older tetracyclines. Randomized controlled trials showed that minocycline 100mg/day for 7 days is as effective as doxycycline 100 mg twice daily for 7 days (Romanowsky B et al 1993).

In the past 10 year doxycycline 100 mg twice daily for 7 days has been seen to be effective in many clinical trials (Robinson AJ et al 2000). The current Centers for Disease Control and Prevention (CDC) Treatment Guidelines recommend doxycycline as primary therapy for C. trachomatis infections in non pregnant women. The recommended regimen is oral doxycycline 100 mg twice daily for 7 days. ( CDC 2002)

For years macrolides constituted an alternative to tetracycline. Erythromycin base 500 mg four times daily for 7 days provided an eradication rate of nearly 100%, but a clinical cure rate of approximately 80% (Toomey KE & Barnes RC 1990). Azithromycin is an azalide/macrolide which is chemically related to erythromycin and has high bioavailability properties which makes it possible to achieve high intracellular levels that are sustained even after a single oral dose (Worm AM & Osterlind A1995).

Several randomized studies have demonstrated that the bacteriological cure rate of a single dose of 1 g was similar to that of doxycycline 100 mg twice daily for 7 days. Azithromycin has few, mild side effects compared to erythromycin and doxycycline. However, although azithromycin is better tolerated, its cost is significantly higher than that of doxycycline. The current CDC Treatment Guidelines recommend azithromycin as primary therapy for uncomplicated *Chlamydia trachomatis* infections in non-pregnant women (CDC 2002).

There is no agreement about the treatment of choice for uncomplicated chlamydial infection in non pregnant women. The two drugs recommended by CDC as primary therapy are doxycycline and azithromycin (CDC 2002) as and alternative therapy, CDC guidelines recommend erythromycin base or erythromycin ethylsuccinate or ofloxacin or levofloxacin. However, azithromycin 1 g single dose is recommended because of the issue of compliance with therapy. Lower doxycycline compliance is a factor that may make azithromycin a better option

The cost effectiveness of treating simultaneously *Chlamydia trachomatis* infection in patient with uncomplicated gonorrhoea was evaluated in a theoretical cohort of 1000 adults. For empirical treatment of uncomplicated chlamydia infection, oral doxycycline 100 mg twice daily for 7 days was more cost effective than a single oral dose of azithromycin 1 g, when doxycycline compliance was greater than 80%. When doxycycline compliance is lower, azithromycin treatment is more cost effective from a social point of view (Genc M & Mardh PA 1997).

## 3.2 Gonorrhoea

### 3.2.1 Overview

Since the 1940s, gonorrhoea has been one of the most frequently reported communicable diseases in the United States (CDC 1997). The rates began to increase in the late 1950s and increase markedly from 1966 to 1975, a period when sexual behaviour pattern were changing dramatically (Barnes RC et al. 1984) However, gonorrhoea has been declining since its 1975 peak due to many efforts, which led to treatment of asymptomatic infected persons and their sexual partners, and interrupting transmission of the infection. Data from nine western European countries between 1991 and 1996 shown there was overall decline in the number of gonorrhoeal cases (J H A Van der Heyden et al. 2000)

Data from the United Kingdom show that the highest rate of gonorrhoea and Chlamydia are in men age 20-24 and women aged 16-19. In the United States, the highest rates are in men aged 20 to 24 and women aged 15-19 and are about 10 fold higher in black people than white people, regardless of sex, comparable with London. (Fox KK. et all 1998). Other risk factors include multiple or casual sexual contacts, sexual activity related to drug use and low socioeconomic status.

N. Gonorrhoea initially infects noncornified epithelium, most often of the urogenital tract and secondarily of the rectum, oropharynx, and conjunctivae. Infection is usually mild but may be asymptomatic. It is transmitted almost exclusively by sexual contact or